

Correspondence

Role of WW domain-containing oxidoreductase in regulating lipid production via AKT signaling in immortalized human sebocytes

Dear Editor,

The human WW domain-containing oxidoreductase (WFOX), a tumor suppressor gene at the common chromosomal fragile site FRA16D at 16q23.3-24.1, has been implicated in various cellular processes, including metabolism, and inflammatory responses. Recent studies suggest its involvement in lipoprotein metabolism, impacting atherosclerosis development.^[1] However, WFOX's role in skin lipid metabolism remains unexplored. The skin surface lipid film, essential for barrier function, consists of keratinocyte- and sebaceous gland-derived lipids. Sebaceous gland dysregulation is linked to inflammatory skin disorders, such as acne, rosacea, seborrheic dermatitis, and hidradenitis suppurativa.^[2] Thus, we aimed to characterize the role of WFOX in lipid synthesis within sebocytes.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (Approval No. 2018-07-059), and written informed consent was obtained from all patients. Primary sebocytes were isolated from sebaceous glands of human skin specimens and immortalized via recombinant retrovirus expressing simian virus 40T antigen (SV40T).^[3] To downregulate WFOX expression, sebocytes were transduced with a recombinant adenovirus expressing a microRNA targeting WFOX (Ad/miR-WFOX). Control cells were transduced with a scrambled microRNA (Ad/miR-Scr). Following transduction, WFOX protein levels were markedly decreased.

To assess WFOX knockdown effects on insulin-like growth factor (IGF)-1-induced lipid production, sebocytes transduced with Ad/miR-WFOX were treated with IGF-1 for 24 h. Lipid extraction and analysis were performed using thin-layer chromatography (TLC), with hexane: diethyl ether: acetic acid (80:20:1) as the solvent system. TLC revealed that WFOX knockdown significantly suppressed IGF-1-induced lipid production, particularly affecting squalene synthesis, while no significant difference was observed in triglyceride levels [Supplementary Figure 1a]. Squalene, a unique component of human sebum, is widely recognized as a key sebum production marker.^[4]

We further investigated whether WFOX knockdown affected lipogenic regulators. Various transcription factors, including peroxisome proliferator-activated receptor (PPAR)- γ , sterol regulatory element-binding protein (SREBP)-1 and SREBP-2, and lipogenic enzymes, such as stearoyl-CoA desaturase (SCD) and farnesyl-diphosphate farnesyltransferase-1 (FDFT-1), regulate sebocyte lipid synthesis. IGF-1 induces SREBP-1 via the IGF-1 receptor (IGF-1R) and downstream pathways.^[5,6] Following Ad/miR-WFOX transduction, sebocytes were treated with IGF-1 for 24 h, and protein levels were evaluated via western blot. WFOX knockdown reduced both basal and IGF-1-induced expression of SREBP-1, SREBP-2, FDFT-1, and SCD. Consequently, IGF-1 failed to upregulate these regulators in WFOX-knockdown sebocytes. Interestingly, WFOX knockdown significantly suppressed PPAR- γ , SREBP-1, SCD, and FDFT-1, but not SREBP-2 [Supplementary Figure 1b], suggesting selective lipid regulation via AKT/mTOR signaling. As SREBP-1 controls fatty acid synthesis and SREBP-2 regulates cholesterol, WFOX may specifically influence sebocyte lipid metabolism.

To further elucidate cellular mechanisms, sebocytes were transduced with Ad/miR-WFOX, treated with IGF-1 for 1 h, and analyzed via western blot for key signaling molecules. WFOX knockdown reduced IGF-1-induced phosphorylation of IGF-1R, AKT, and mTOR, while extracellular regulated protein kinase (ERK) phosphorylation remained unaffected [Supplementary Figure 1c]. These findings suggest that WFOX knockdown-mediated lipid suppression is AKT/mTOR-dependent, rather than ERK-mediated [Supplementary Figure 1d]. All experiments were performed in triplicate, and the data were analyzed using GraphPad Prism Version 8.3.0 (GraphPad Software Inc.; San Diego, CA, USA). Statistical significance was determined using Student's *t*-test ($P < 0.05$). The PI3K/AKT/mTOR pathway, primarily known for its role in cancer cell survival, is also implicated in inflammatory skin diseases, including acne, rosacea, and hidradenitis suppurativa. Notably, AKT hyperactivation promotes sebum production and inflammation, key factors in acne pathogenesis. Dysregulated AKT signaling is also linked to immune-mediated skin disorders, suggesting broader involvement in cutaneous

inflammation.^[7] Moreover, WWOX mutations have been linked to genetic disorders such as WWOX-related encephalopathies, which frequently present with dermatological manifestations like pigmentary abnormalities and skin rashes.^[8] Increasing evidence suggests a close interaction between WWOX and the AKT/mTOR pathway, indicating that WWOX dysfunction may contribute to dermatological diseases through AKT dysregulation. Given its role in AKT signaling, further research is warranted to explore WWOX's potential impact on inflammatory and genetic skin disorders.

Our study has certain limitations. First, *in vitro* sebocyte model may not fully reflect lipid metabolism and inflammation in human skin. Second, while our results demonstrate WWOX's regulatory role in sebocyte lipid metabolism and AKT signaling, *in vivo* validation is required to confirm these effects. Potential variability in sebocyte responses should be considered. Future studies incorporating *in vivo* models and patient-derived sebocytes will be essential to clarify WWOX's role in dermatological disorders.

In summary, our study identifies WWOX knockdown as a regulator of sebocyte lipid production, affecting lipogenic regulators and AKT signaling. These findings highlight WWOX's role in lipid metabolism and provide insights into sebocyte biology. To our knowledge, this is the first study investigating WWOX's intracellular signaling in skin lipid metabolism. Further research is needed to explore WWOX's therapeutic potential in sebaceous gland-associated skin disorders, such as acne, rosacea, and hidradenitis suppurativa.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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